Chapter 6
An Evolutionary Functional Analysis of the Hormonal Predictors of Women's Sexual Motivation

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Introduction

What is the evolved function of women's sexual motivation? Recent research suggests that low sexual desire is a common condition among women, with rates of occurrence in the 20–40 % range even among premenopausal women (Gracia et al. 2007; Laumann et al. 1999; Stuckey 2008). The medical and scientific literatures have often treated low desire as a clinical disorder, with hypoactive sexual desire disorder codified as a recognized condition in the DSM-IV (4th ed., text rev.; *DSM-IV-TR*; American Psychiatric Association 2000). An important question from a functional perspective, however, is whether low desire is a disorder in the sense of brain mechanisms failing to operate as designed, or simply with respect to desired outcomes. It is not clear, for instance, that fairly constant, uninterrupted desire would have promoted women's reproductive success on average over the course of human evolution. Understanding both between-women and within-woman variance in desire would seem to require knowledge of the functional design of the brain mechanisms that regulate sexual motivation. Surprisingly, this issue of functional design has been largely ignored in both the medical and scientific literatures on human sexuality. This chapter will analyze women's sexual motivation from a functional perspective, with specific emphasis on the role of hormonal signals in the regulation of desire.

The chapter will also take a comparative approach to understanding women's sexual motivation. The physiology of the human menstrual cycle exhibits extensive parallels to that observed in the cycles of nonhuman primates, and broader homologies between human and nonhuman motivational systems (e.g., Roney and Maestripieri 2002) make it reasonable to suppose that the mechanisms that regulate human sexual motivation will be variations on designs found in nonhuman species.

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This comparative perspective may help frame the issue of functional design in ways that may be obscured in the extant medical literature on human sexuality. As reviewed below, for instance, most nonhuman mammalian females are only sexually receptive on days of the estrous cycle when conception is possible, and thus by comparison the relevant functional question regarding women's sexuality is not why desire is so low but instead why it appears to be so much more frequent than in other species.

The plan for the chapter is to first review the endocrine events associated with estrous cycles in order to describe the types of functional information that may be carried by hormonal signals. A basic sketch of possible functions of sexual motivation will follow, which will then be used to generate predictions regarding which combinations of hormonal signals should predict variations in sexual motivation given specific functional hypotheses. A brief review of the nonhuman literature regarding hormonal regulation of female sexual behavior will then provide evidence regarding which functions are consistent with the extant data. Finally, the question of hormonal regulation of female sexual motivation will be applied to humans, with specific emphasis on a new study that addressed this question in natural menstrual cycles (Roney and Simmons 2013) and was the focus of my presentation at the 2013 Oakland University "Evolution of Sexuality" conference. Although this study suggests similarities between human and nonhuman females in the hormonal regulation of sexual motivation, there remain questions regarding uniquely human components of women's sexual desire, and the chapter will include a brief discussion of future research that may address those questions.

Cycle Phase Physiology and Hormones as Information

Physiology of the Human Menstrual Cycle

The hormonal events associated with mammalian female reproductive cycles are well-understood, and the dynamics of the human menstrual cycle will be summarized as an example here (for reviews, see Fauser and Van Heusden 1997; Hall 2004; Strauss and Williams 2004). Human females produce all of their gametes prenatally, which are stored in a resting pool as oocytes until recruited for final stages of maturation. "Follicles" refer to oocytes and the support cells that surround them. At a rate of approximately 1000 follicles per month, beginning even before birth, follicles are recruited out of the resting pool and begin to develop via the replication of the support cells. Follicle stimulating hormone (FSH) is a signal from the pituitary gland necessary for the continued development of follicles, and without this signal, follicles undergo a type of programmed cell death. FSH production at levels high enough to stimulate continued follicle development occurs at puberty with maturation of the hypothalamic–pituitary–gonadal axis. When FSH exceeds a threshold, follicle support cells replicate and eventually begin to express aromatase, the enzyme that produces estrogen from androgen precursors. The follicle

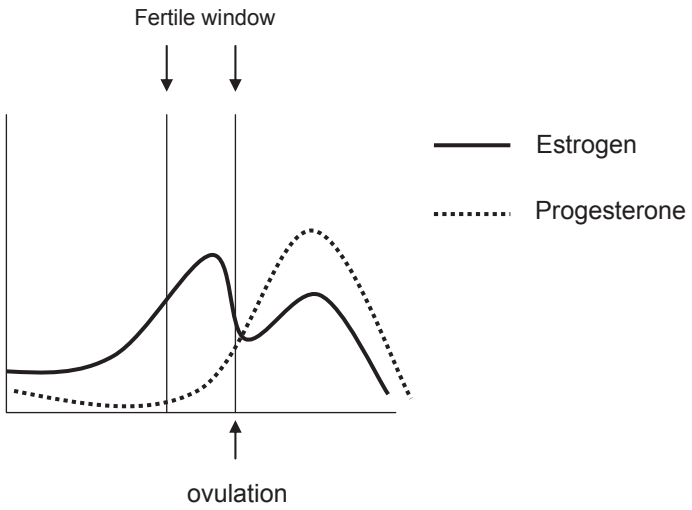

Fig. 6.1 Depiction of prototypical estrogen and progesterone concentrations across days of ovulatory menstrual cycles

that reaches a replication stage at which estrogen production begins also increases expression of luteinizing hormone (LH) receptors, which facilitate continued follicular development even absent FSH. Because estrogen has a negative feedback effect on FSH release, estrogen production from the first follicle that reaches this stage reduces the FSH signal to other developing follicles, and this in combination with other inhibitory signals leads the other follicles to die such that one oocyte and its surrounding support cells become the "dominant" follicle.

As cell replication continues in the dominant follicle, its support cells produce a steep rise in estrogen concentrations. This rise in estrogen in turn activates a surge in LH production from the pituitary, which causes rupture of the follicle and subsequent release of the ovum for possible fertilization. The support cells from the follicle then become a new structure called the corpus luteum, which secretes estrogen and progesterone in the second half of the cycle after ovulation. Rising estrogen before ovulation stimulates development of the uterine lining for possible implantation of a zygote, whereas corpus luteum production of estrogen and especially progesterone is necessary for the uterine lining to provide a nutritive environment.

The above sequence of events produces a prototypical pattern of estrogen and progesterone production in human ovulatory cycles that is summarized in Fig. 6.1. Progesterone is typically low in the follicular phase (the region of the cycle preceding ovulation) but then exhibits large peaks via corpus luteum production in the luteal phase (the region of the cycle after ovulation but preceding the next menstruation). Estrogen also begins low early in the follicular phase but then rises sharply with dominant follicle growth, peaks just before ovulation, falls sharply, and then rises again to a secondary but usually smaller peak in the luteal phase. Testosterone is a third hormone produced by the ovary as it serves as a precursor to estrogen

production via the aromatase enzyme. About half of testosterone production comes from the ovary in ovulatory cycles (with the other half derived from adrenal androgen production; see Abraham 1974; Burger 2002), and several studies have reported midcycle testosterone peaks associated with the preovulatory estrogen surge, followed by fairly low testosterone production in the luteal phase (e.g., Abraham 1974; Campbell and Ellison 1992; Roney and Simmons 2013; Van Goozen et al. 1997). Importantly, the patterns depicted in Fig. 6.1 apply to ovulatory cycles, but when dominant follicle development is inhibited (as occurs during lactational amenorrhea, for example), estrogen and progesterone concentrations remain consistently low across time.

Information Content of Hormones in Human Menstrual Cycles

Although estrogen and progesterone have important signaling functions related to endometrial development within the reproductive tract, they are also released into the general circulation whereby they can reach brain mechanisms and thus provide information that can be used by psychological mechanisms that regulate behavior. What information do these hormones carry? Information related to fecundity (i.e., the probability of successful conception and gestation given unprotected intercourse) may be especially important, at two broad timescales. First, at a *within-cycle* timescale, estrogen and progesterone can signal time in the cycle when conception is possible. Conception is only possible within a narrow window from about 5 days before ovulation through the day of ovulation itself (e.g., Wilcox et al. 1998), which is a time period characterized by steeply rising estrogen but also fairly low progesterone (Fig. 6.1 provides a schematic depiction of the fertile window relative to hormone production). High estrogen combined with low progesterone may therefore signal elevated conception risk. Conception appears to be impossible during the luteal phase when progesterone exhibits pronounced peaks within ovulatory cycles, and thus high progesterone concentrations may provide an especially strong signal of low immediate conception risk. The information carried by testosterone is more ambiguous. Although testosterone on average exhibits a midcycle peak and reduced luteal phase production, the substantial adrenal sources of this hormone may cloud its signal value with respect to fecundity. As such, a priori, one would expect brain mechanisms to be designed to rely primarily on estrogen and progesterone as clearer signals of conception risk, though it is possible that testosterone elevations might supplement information carried by estrogen if larger dominant follicles produce greater amounts of both hormones.

Ovarian hormones may also carry information regarding fecundity at what could be thought of as a *between-cycle* (or lifespan) time scale. Although premenopausal women in industrialized countries tend to experience frequent ovulatory cycles due to both late marriage and the use of contraception, women in natural fertility populations thought to be more similar to human ancestral environments cycle much more rarely due to suppression of ovulation associated with events like lactation

or food shortage (see Ellison 2001; Strassmann 1997). As such, throughout most of human evolution, women likely spent most of their reproductive lives with low ovarian hormone concentrations, with fecund cycles occurring only rarely between the end of lactational amenorrhea and the conception of the next child. Even within ovulatory cycles, however, evidence suggests that fecundity varies across cycles within the same women, with higher probabilities of conception in cycles with higher estrogen production (e.g., Lipson and Ellison 1996; Venners et al. 2006). In Fig. 6.1, then, imagine a second estrogen curve superimposed higher than the one depicted: for the same woman, fecundity would on average be greater in the cycle associated with the higher curve.

Throughout most of human history, therefore, elevated ovarian hormone concentrations may have signaled that a woman was experiencing one of the rare ovulatory cycles that occurred between longer stretches of anovulation (estrogen and progesterone are also highly elevated during pregnancy, but it seems likely that brain mechanisms are designed to distinguish pregnancy from ovulatory cycles). The information content of progesterone is especially interesting in this context since elevated progesterone would have provided opposite signals of fecundity at the within- and between-cycle timescales: whereas high progesterone concentrations signaled luteal timing and thus zero immediate fecundity, they also signaled that a woman was experiencing fecund cycles in which behaviors related to mating and sexuality may have assumed greater functional importance due to elevated probability of conception in near-future cycles. In other words, in humans, progesterone may act as a within-cycle signal of low fecundity but a between-cycle signal of high fecundity. Estrogen, on the other hand, should signal greater fecundity at both the within- and between-cycle timescales.

Functional Hypotheses Regarding the Endocrine Regulation of Sexual Motivation

Within-Cycle Predictions

A basic functional expectation is that female sexual motivation will be higher on cycle days for which conception is possible than on cycle days with negligible conception risk. This idea is predicated on the assumption that sexual behavior has recurrently entailed costs to females in terms of time, energy, risk of injury, risk of sexually transmitted disease and, in group-living species, perhaps also social costs in the form of harassment from other individuals (see Wallen 2001). Conception would have provided a countervailing fitness benefit. Other things equal, then, a first-order prediction is that females will be designed to avoid the costs of sex when the benefit of conception is absent but then exhibit enhanced sexual motivation (in the form of heightened receptivity and/or proceptivity) when conception is possible. In species in which males provide no benefits to females other than genetic

material carried in sperm—which characterizes most mammals—this logic predicts that females will exhibit essentially zero sexual motivation outside of cycle days when conception is possible. In species in which males provide nongenetic material benefits, however, other things may often not be equal, and female sexual behavior may have functions related to the acquisition of these material benefits that makes predictions about the determinants of sexual motivation more difficult.

Considering first species in which males do not provide nongenetic benefits, the expectations regarding the endocrine regulation of sexual motivation are straightforward in that sexual behavior should be promoted by hormones that positively predict current fecundity but inhibited by hormones that negatively predict it. In all nonhuman mammals, estrogen is associated with follicle development and ovulation and thus estrogen should be a consistent positive predictor of sexual motivation in species without extended sexuality. In most nonhuman mammals, an extended diestrus similar in biology to the above described human luteal phase is associated with both zero immediate fecundity and enhanced progesterone production, leading to the prediction of an inhibitory effect of progesterone on sexual motivation. Most rodents are an exception, however, in which a fully formed corpus luteum occurs only in the case of conception (or pseudopregnancy), and progesterone peaks before ovulation and relatively soon after the estrogen peak, at a time when conception is possible (for reviews, see Carter 1992; Blaustein 2008). As such, rodents provide an interesting test case for the informational signaling content of hormones since progesterone (at least when not pregnant) should facilitate rather than inhibit sexual behavior. Finally, the expected effects of testosterone on sexual motivation are ambiguous due to its uncertain information content.

In species in which males provide nongenetic benefits to females—such as food, protection, grooming, and paternal care—females often exhibit "extended sexuality," which refers to sexual receptivity and/or proceptivity on cycle days for which conception is not possible (for an extensive and insightful discussion of extended sexuality, see Thornhill and Gangestad 2008). In chimpanzees, for instance, females mate promiscuously on follicular phase days outside of the fertile window, which has been explained as a paternity confusion device that decreases the probability that males will mistreat a female's offspring (for a review, see Emery Thompson 2009). Human females exhibit pronounced extended sexuality, with sexual behavior occurring at all times of the menstrual cycle. Various theories have proposed that extended sexuality in conjunction with concealed ovulatory timing may have evolved within the context of human pair-bonding as a means of promoting men's continued proximity to and material investments in their partners, since males would likely eschew such investment and instead compete to inseminate currently fertilizable females under conditions in which ovulatory timing could be precisely detected (see Alexander and Noonan 1979; Strassmann 1981; Symons 1979). If some version of these theories is correct, then one expects women's extended sexuality to be designed to have promoted the flow of nongenetic benefits from male partners within the context of relationship initiation and maintenance. Precisely what this design might be has been a neglected topic in the study of human sexuality. Grebe et al. (2013) presented evidence that women were more proceptive (i.e.,

initiated sex more often) during the luteal phase when they were more invested in their relationship than their long-term partners, which the authors interpreted as a means of motivating greater male investment. Overall, however, little is understood regarding the predictors of extended sexuality.

Although extended sexuality complicates the story considerably, I predicted that estrogen would be a positive predictor of women's sexual motivation at a within-cycle timescale. Women's extended sexuality could be regulated by nonhormonal mechanisms that are not linked to fecundity, such that hormonal and nonhormonal mechanisms operate concurrently. Whatever the determinants of extended sexuality, then, the arguments for greater sexual motivation during fecund cycle days still applies to humans, as the costs of sex should, other things equal, produce design for reduced sexual motivation on days when conception is not possible. My expectations regarding the effects of progesterone on women's sexual motivation were less certain: whereas progesterone clearly signals low fecundity within-cycles, it might also act as a positive signal of fecundity at the between-cycle timescale (see below).

Between-Cycle Predictions

Motivational systems function to allocate attention and behavioral effort to those adaptive problems that are currently most pressing. Many of the conditions under which ovarian hormones are reduced in humans at the between-cycle (or lifespan) timescale involve adaptive problems that demand immediate behavioral effort. During intensive lactation, for instance, a shift in attentional and behavioral resources away from sexuality and toward maternal care appears especially functional, and indeed evidence suggests that lactation is associated with a substantial decrease in women's libido (e.g., Avery et al. 2000; Forster et al. 1994; Rupp et al. 2013). As reviewed above, conditions such as lactation, negative energy balance secondary to food shortage, as well as menopause, are all associated with decreases in ovarian hormones such that elevated estrogen and progesterone could signal that a woman is experiencing a life stage during which sexuality takes on greater importance and should thus be allocated increased attention and motivation.

Whether calibration of sexual motivation to between-cycle fluctuations in ovarian hormones should extend to days outside of the fertile window is unclear. At issue is whether, for instance, a luteal phase day in a high-estrogen cycle should be treated differently by brain mechanisms than a luteal phase day in a low-estrogen cycle: immediate fecundity is zero on both days, but the general problem of mating and reproduction may be more important in a life stage sense in the higher estrogen cycle with greater fecundity. Increased sexual motivation across days of more fecund cycles could have functions related to mate-seeking or mate-evaluation during time periods when conception is more likely to occur in the near future, for example, or could signal paternity confidence to a partner through increased sexual behavior near the time of conception. The possibility of between-cycle effects of ovarian hormones even outside of the fertile window led me to hypothesize that estrogen

will be the primary endocrine regulator of women's sexual motivation, because estrogen is positively correlated with fecundity at both within- and between-cycle timescales. If there were benefits to increased sexual motivation in more fecund cycles, then inhibitory effects of progesterone might disrupt between-cycle calibration of libido to fecundity, which led to the expectation that progesterone may not be a consistent regulator of sexual motivation in humans. Thus, although sexual desire may decrease in the luteal phase relative to the fertile window, my expectation was that this effect would be mediated by estrogen rather than progesterone.

Empirical Evidence for Hormonal Predictors of Female Sexual Motivation

Nonhuman Mammals

Estradiol and Progesterone

In domestic ruminants (e.g., sheep, cows, horses, pigs) in which males typically provide no nongenetic benefits and females experience a nonfecund diestrus phase associated with elevated progesterone, sexual activity is mostly confined to a behavioral estrous period during which conception is possible, estradiol (the dominant circulating form of estrogen in mammals) is necessary for and promotes female sexual behavior, and progesterone inhibits the current expression of sexual behavior (for reviews, see Beach 1976; Crowell-Davis 2007; Fabre-Nys and Gelez 2007; Katz 2007; Pedersen 2007). In rodents such as rats and mice, estradiol also promotes sexual receptivity (for reviews, see Carter 1992; Pfaff et al. 2002), but progesterone likewise facilitates the expression of sexual behavior after obligatory estrogen priming; in fact, the standard procedure for inducing sexual receptivity in ovariectomized rodents is injection of estradiol about 48 h prior to sexual testing followed by a progesterone injection within a few hours of such tests (e.g., Blaustein 2008; Powers 1970; Whalen 1974). Because elevated progesterone signals impending ovulation in rodents but not in ruminants, this contrast in the effects of progesterone on sexual motivation provides comparative evidence that brain mechanisms use hormones as signals of fecundity for the purpose of regulating sexual behavior. The differing effects of progesterone likewise demonstrate evolutionary plasticity in the signaling function of the same chemical in different species, which leaves open the possibility that progesterone could either promote or inhibit sexual motivation in women, depending on its information content.

Females of many nonhuman primate species, in contrast to other mammals, are sometimes sexually receptive outside of fecund cycle days and may even mate when ovariectomized (at least in captive conditions), leading to the idea that primate sexual motivation has been released from strict hormonal control (for reviews, see Dixson 1998; Wallen 2001). Nonetheless, extensive evidence supports greater sexual motivation during cycle days when estradiol is elevated and progesterone is

low. In rhesus macaques—the most extensively studied nonhuman primate—sexual behavior under group housing conditions correlates strongly and positively with estradiol concentrations, but strongly and negatively with progesterone concentrations (Wallen et al. 1984). Likewise, manipulations of estradiol promote female sexual receptivity and proceptivity (e.g., Michael et al. 1978; Zumpe et al. 1983), and positive effects on female sexual initiation have been demonstrated even with unresponsive males tested during the nonbreeding season, thus ruling out changes in male behavior as the cause of increased sexual interactions (Zehr et al. 1998). Experimental manipulations of progesterone are less common in nonhuman primates, and as such decreases in luteal phase sexual behaviors could be caused by decreases in estradiol rather than by correlated increases in progesterone. Kendrick and Dixson (1985), however, demonstrated in marmosets that progesterone administration increased refusals of male mount attempts and decreased receptive and proceptive tongue-flicking displays relative to ovariectomized females without progesterone, whereas the opposite outcomes were obtained via administration of estradiol.

In ape species, extended sexuality is the most pronounced among nonhuman mammals, though evidence likewise implicates positive and negative effects of estradiol and progesterone, respectively, on female sexual behavior (for a review, see Emery Thompson 2009). Sexual behavior in chimps and bonobos generally coincides with expression of sex skin swellings, which appear to be promoted by estrogen but inhibited by progesterone (see Deschner et al. 2004; Emery and Whiten 2003; Heisterman et al. 1996); indeed, copulations in chimps tend to cease after the luteal phase rise in progesterone triggers sex skin detumescence (e.g., Deschner et al. 2004). These patterns are difficult to interpret in terms of female motivation in chimps given high rates of male sexual coercion in this species (Muller et al. 2007), but such coercion appears absent in bonobos in which females nonetheless accept more male copulation attempts when swollen than when not, which suggests greater receptivity when estradiol is higher (Furuichi and Hashimoto 2004). Female proceptivity in gorillas and orangutans appears to peak near the cycle peak in estradiol and testosterone, but ends abruptly with the rise in luteal phase progesterone (reviewed in Emery Thompson 2009).

Overall, then, the same hormonal correlates of sexual behavior are found in mammalian species with and without extended sexuality, namely positive associations with estradiol and negative associations with progesterone. The main difference between these groups may be in the extended time-course of estrogen production (or sensitivity) during the follicular phase in many primate species. Female chimpanzees and bonobos are in estrogen-dependent, highly swollen states for 10–12 days per cycle on average, and are partially swollen for even longer, despite the fact that maximum fecundity is probably restricted to the few days preceding and including the day of ovulation (Deschner et al. 2004; Heisterman et al. 1996). Thus, although extended sexual receptivity associated with prolonged sexual swellings must have nonconceptive functions, it appears that the endocrine mechanisms for it have been conserved from species with more transient periods of behavioral estrous.

Testosterone

In contrast to the clear roles of estradiol and progesterone in female sexual motivation among nonhuman mammals, the role of testosterone is less certain. Receptivity can be primed in ovariectomized females of many species without testosterone administration, which demonstrates that ovarian testosterone is not a necessary signal. Nonetheless, some evidence in rodents suggests that testosterone may produce synergistic effects with estradiol and other signals to produce higher levels of proceptivity than found without testosterone administration (e.g., Fernandez-Guasti et al. 1991). An early literature provided evidence for positive effects of androgens on the sexual receptivity of ovariectomized female macaques in captive pair tests (reviewed in Wallen 2001), but subsequent research provided strong evidence for estradiol as the primary positive regulator of sexual motivation in female macaques. Studies that induced artificial menstrual cycles in ovariectomized females via cyclic administration of estradiol, progesterone, and testosterone, for instance, demonstrated that estradiol promoted female sexual behavior but that omission of testosterone from the artificial cycles had no effects on sexual motivation (Michael et al. 1978; Zumpe et al. 1983). In addition, positive effects of androgens on sexual receptivity appear to require aromatizable androgens (e.g., Wallen and Goy 1977), suggesting that androgens may exhibit positive effects via conversion to estrogens.

At most, then, testosterone may supplement the positive effects of estradiol in the regulation of some components of mammalian female sexual motivation. That estradiol and progesterone appear to be the more important signals makes functional sense given that these hormones provide clear information regarding fecundity via their links to follicle development and corpus luteum formation. As explained earlier, it is less clear what functional information is provided by testosterone over the course of female reproductive cycles.

Humans

Between-Cycle (Lifespan) Timescale

Extant evidence for the role of ovarian hormones in women's sexual motivation has addressed effects of hormones at various time-scales. Perhaps the strongest evidence for hormonal regulation of libido has been at the lifespan timescale with respect to menopause and the partial reversal of its effects via hormone replacement therapy. Several studies have provided convergent evidence that sexual motivation decreases after natural or surgical menopause (Alexander et al. 2004; Dennerstein et al. 1977, 2005; Gracia et al. 2007), and additional evidence supports the efficacy of hormone replacement therapy in increasing sexual desire in menopausal women via use of estrogen (Dennerstein et al. 1980; Nathorst-Boos et al. 1993; Sherwin 1991; Wiklund et al. 1993), testosterone combined with estrogen (Braunstein et al. 2005; Floter et al. 2002; Sherwin et al. 1985), or testosterone alone (Davis et al. 2008). Although positive effects of both estrogen and testosterone provide ambiguous

evidence regarding which signal may be most important in natural cycles (especially since testosterone can be converted to estrogen), these studies provide clear support for hormonal influences on the regulation of women's sexual motivation.

Other lines of evidence suggest that declining estrogen may be the key hormonal determinant of menopausal decreases in sexual motivation. First, in natural menopause, testosterone does not usually change significantly (beyond the gradual decrease with age), and in fact the decrease in sex hormone-binding globulin (SHBG) that occurs at menopause leads to an increase in free androgens (see Burger 2002); thus, decreases in sexual motivation at natural menopause occur in an endocrine context characterized by reduced estrogen but increased free testosterone. Second, studies that have followed women longitudinally across the menopausal transition have produced evidence that changes in sexual functioning are predicted by changes in estradiol but not by changes in androgens (Dennerstein et al. 2002, 2005; Freeman et al. 2007; McCoy 1990). Dennerstein et al. (2005) demonstrated that estradiol had a positive effect on sexual responsiveness that was independent of relationship factors such as feelings for the partner and acquisition of a new partner, both of which were positive predictors of sexual motivation. They concluded from their study: "…the effect of the menopausal transition on sexual function is overwhelmingly caused by the marked decline in E_2" (p. 179).

Decreases in sexual motivation attributable to menopausal declines in estradiol are consistent with the hypothesis that estradiol calibrates sexuality at between-cycle or lifespan timescales. The large and extended decline in estradiol may signal a nonreproductive lifestage during which the benefits of sex over evolutionary time were reduced on average, thus increasing the cost–benefit ratio of sexual behavior. Reduced sexual motivation at this time may not only have reduced the costs of sexual behavior but also functioned to reallocate attention and motivation toward those adaptive problems that were more fitness relevant at this lifestage: in particular, a shift in attention from mating and sexuality to investment in kin. Benefits of nonconceptive sex associated with extended sexuality may still have been present after menopause (if sex had positive effects on pair-bond maintenance and thus promoted male investment in descendants, for instance), although the mechanisms regulating this are unclear and may include nonhormonal signals.

Although the data on menopause are consistent with between-cycle hormonal regulation of sexual motivation, menopause is an extreme case of extended hormone deprivation and it is unclear whether between-cycle fluctuations in estradiol would calibrate sexual motivation in premenopausal women. Chemical suppression of ovarian hormone concentrations over an 8-week period led to large decreases in self-reported sexual functioning in a sample of healthy premenopausal women (Schmidt et al. 2009), which indicates that minimum hormone concentrations are necessary for normal sexual motivation in premenopausal women. In that study, 4 weeks of estradiol or progesterone replacement had not fully restored sexual function, though there was a positive trend for effects of estradiol and mechanisms related to sexual motivation could have "fast off, slow on" design properties such that positive effects of estradiol might have been found had treatment continued longer. No previous studies have followed premenopausal women across multiple natural

cycles to test whether sexual desire is higher in cycles with higher estradiol concentrations, however, and this was thus one of the goals of the research presented later in this chapter.

Within-Cycle Timescale

A second line of evidence for the role of ovarian hormones in women's sexual motivation comes from studies that have measured changes in sexual behavior or subjective desire associated with phases of the menstrual cycle. A large number of studies have provided evidence that measures of sexual motivation are higher near ovulation (i.e., inside the fertile window) than at other times of the cycle (e.g., Adams et al. 1978; Bullivant et al. 2004; Dennerstein et al. 1994; Diamond and Wallen 2011; Harvey 1987; Matteo and Rissman 1984; Pillsworth et al. 2004; Stanislaw and Rice 1988; Wilcox et al. 2004). A number of these studies have detected increased sexual initiation by women or increased subjective desire, suggesting that these effects cannot be explained simply by greater male interest near ovulation (in fact, rates of male initiation appear to be relatively constant across the cycle; e.g., Van Goozen et al. 1997). Despite this evidence, there have been some failures to replicate the midcycle increases in sexual motivation (for a review, see Regan 1996), though studies that have more precisely verified the timing of ovulation via frequent hormone sampling or LH tests appear to be fairly consistent in demonstrating periovulatory peaks (e.g., Bullivant et al. 2004; Dennerstein et al. 1994; Diamond and Wallen 2011; Wilcox et al. 2004).

Increased sexual motivation near ovulation supports the calibration of women's libido to within-cycle fluctuations in fecundity, but does not precisely address which combination of hormonal signals might produce these effects. Only a small number of studies have measured hormone concentrations across broad regions of the cycle in order to test for associations with measures of sexual motivation in natural menstrual cycles (Dennerstein et al. 1994; Morris et al. 1987; Persky et al. 1978a, b; Van Goozen et al. 1997). None of these studies reported significant within-cycle relationships between fluctuations in hormone concentrations and fluctuations in sexual desire or behavior. A number of studies did report that women with higher average or midcycle testosterone exhibited higher frequencies of sexual behavior (Morris et al. 1987; Persky et al. 1978b; Van Goozen et al. 1997; c.f., Bancroft et al. 1983), which provides evidence for a between-women effect of androgens (but see Wallen 2001, for a reanalysis of the data in Persky et al. 1978a, b that suggests positive between-women associations between estradiol and measures of women's sexual initiation). The null effects in these studies at the within-cycle timescale leave unspecified the physiological signals that may regulate cyclic shifts in libido.

Various methodological issues may have limited the conclusiveness of the studies that tested within-cycle hormonal correlates of sexual motivation. Sample sizes were small, raising issues of power, and most of the articles were published before the widespread use of multilevel regression modeling, which both increases power in within-subject analyses (relative to some alternative

approaches) and correctly accounts for correlated error terms given nested data. In addition to small numbers of subjects, hormone sampling was typically infrequent; only univariate analyses were performed, with no studies having tested the effects of particular hormones while controlling for the effects of other hormones; and only same-day associations between hormones and outcome variables were tested despite the possibility of time delays for the genomic effects of ovarian hormones. Given these limitations, my lab implemented a large study designed to provide further evidence regarding the hormonal predictors of sexual motivation in natural menstrual cycles.

New Research on Hormonal Predictors of Women's Sexual Motivation

This section summarizes the methods and findings from a recent study on the hormonal predictors of women's sexual motivation (Roney and Simmons 2013). We attempted to secure data regarding both within- and between-cycle hormonal predictors of sexual desire and behavior by collecting daily measures from women across two different menstrual cycles. This allowed more comprehensive tests of within-cycle relationships between ovarian hormones and sexuality, as well as the first tests in premenopausal women of whether sexual motivation is higher in cycles with higher vs. lower average concentrations of particular hormones.

Summary of Methods

Our final sample with available hormone data included 43 undergraduate women who self-reported being heterosexual and naturally cycling (mean age = 18.76 years). Thirty-six women collected daily saliva samples across two full menstrual cycles (separated by 1–2 months), while seven completed data collection for only the first cycle. In addition to collecting saliva samples, participants logged on to a secure website each day to complete survey measures.

Two primary dependent variables were the focus of the present report, one assessing subjective sexual desire and the other assessing sexual behavior. The desire item read: "How much did you desire sexual contact?" and was assessed on a 1–7 scale. The behavior item was a yes/no assessment of whether sex occurred that day, with sex defined as "intercourse or other forms of genital stimulation with another person." Additional items inquiring whether the woman or her partner initiated sex, as well as whether masturbation occurred, are described in Roney and Simmons (2013).

Saliva samples were assayed for estradiol, progesterone, and testosterone (intra- and interassay CVs were below 10% for each hormone). All samples in a 9-day window centered on an initial estimate of the day of ovulation were sent for assay,

as were samples from alternating days outside of this window (3621 total assays). Once hormone values were available, the day of ovulation was re-estimated based on the conjunction of the midcycle estradiol drop and the beginning of the luteal phase increase in progesterone.

Data analyses employed multi-level regression models, which allowed tests of within-cycle (Level-1) predictors of sexual motivation (e.g., do day-to-day fluctuations in estradiol predict within-cycle fluctuations in desire?); within-women, between-cycle (Level-2) predictors (e.g., does change in average estradiol across the same woman's two cycles predict change in her average sexual motivation?); and between-women (Level-3) predictors (e.g., do women with higher estradiol on average report higher desire on average?). We predicted that estradiol would positively predict our measures of sexual motivation at all three levels, based on the positive links between estradiol and fecundity at both within- and between-cycle timescales. All three hormones were entered simultaneously into the regression models, giving each equal opportunity to predict the dependent variables. At Level-1 (within-cycle timescale), we constructed separate regression models testing the effects of current day, 1-day lag, and 2-day lag hormone concentrations to account for possible time delays in the effects of ovarian hormones. As mentioned earlier, estrogen administration primes sexual receptivity in female rodents at a time lag of approximately 48 h, and based on those findings we expected the strongest effects at a 2-day lag.

Summary of Results

At the within-cycle (Level-1) level of analysis, estradiol measured 2 days earlier was a positive predictor of current day subjective sexual desire, $b = 0.16$, $p = 0.01$, whereas current day estradiol had a marginally significant effect, $b = 0.09$, $p = 0.096$. Unlike estradiol, we had not predicted significant effects of progesterone, but found strong evidence for negative associations with sexual desire at all three timescales: two-day lag, $b = -0.20$, $p = 0.0001$; one-day lag, $b = -0.11$, $p = 0.04$; current day: $b = -0.13$, $p = 0.01$. There were no significant effects of testosterone at any timescale.

Figure 6.2 plots estimated sexual desire against estimated day of the cycle, with cycles aligned on the day of ovulation as day zero. Progesterone concentrations are also plotted on the secondary y-axis. It can be seen, first, that there was a visible decrease in sexual desire just as progesterone was reaching its highest luteal phase values. Second, although less obvious visually, there was a significant within-cycle effect of fertile window timing (days −5 to 0) on sexual desire, with higher desire on average inside the fertile window (mean = 3.74) than on other days (mean = 3.48), $b = 0.26$, $p = 0.023$. Furthermore, the rise in luteal progesterone mediated the decrease in desire when moving from the fertile window to the luteal phase, whereas estradiol and testosterone did not mediate this pattern (for statistical details, see Roney and Simmons 2013). These results are consistent with progesterone acting as a within-cycle stop signal that truncates the midcycle rise in sexual motivation.

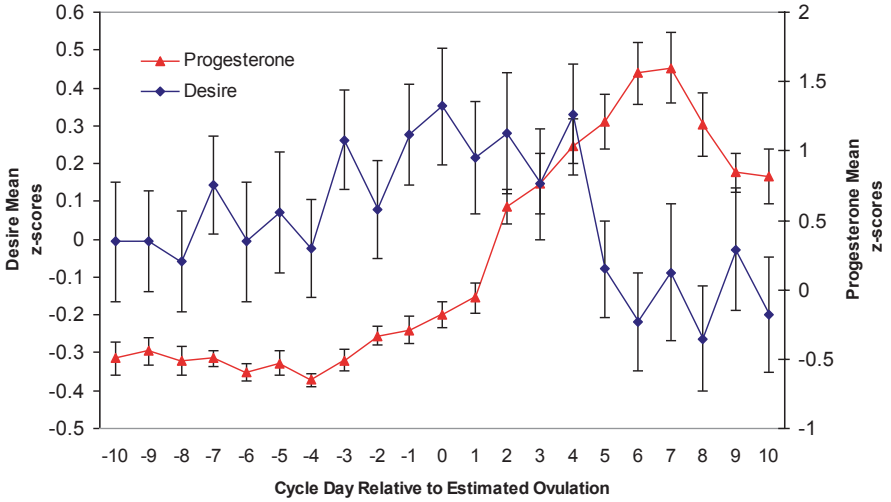

Fig. 6.2 Mean desire for sex and mean progesterone concentrations aligned against estimated day of cycle, where day zero represents the estimated day of ovulation. Values are standardized within-cycles such that zero points on the y-axes represent the mean values within a given cycle. *Error bars* are SEM

One other variable was a within-cycle predictor of self-reported desire: weekend timing. Figure 6.3 plots average sexual desire against day of the week. It can be seen, first, that Monday was a poor day for desire. Friday and Saturday were associated with pronounced increases in desire, on average, and a binary weekend variable comparing Friday and Saturday to other days of the week was a significant within-cycle predictor of desire, $b = 0.40$, $p < 0.0001$. The weekend timing and hormone variables were independent of one another and did not interact in the prediction of sexual desire.

There were no significant effects of any hormone at the within-woman, between-cycle or between-women levels of analysis. Thus, contrary to our prediction, among participants with two cycles of data, women did not experience higher desire on average in the cycle with higher mean estradiol. Variance in hormone concentrations was restricted at the between-cycle level, however, as hormone values were similar on average within-women across their two cycles. Thus, although we found no evidence for between-cycle calibration of desire to hormone concentrations, more rigorous tests of such calibration may require following women across cycles with larger differences in hormone concentrations than those observed in this study.

For sexual behavior, logistic mixed regression models were used to model the probability of sex on given response days. Two variables were significant predictors at the within-cycle level of analysis. Current day estradiol positively predicted the probability of sex, with a one standard deviation increase in estradiol associated with a 34% increase in the odds of sex relative to other days in the same cycle ($p = 0.02$). Weekend timing was also a positive predictor, with the odds of sex approximately three times greater on weekend days relative to weekdays ($p < 0.0001$).

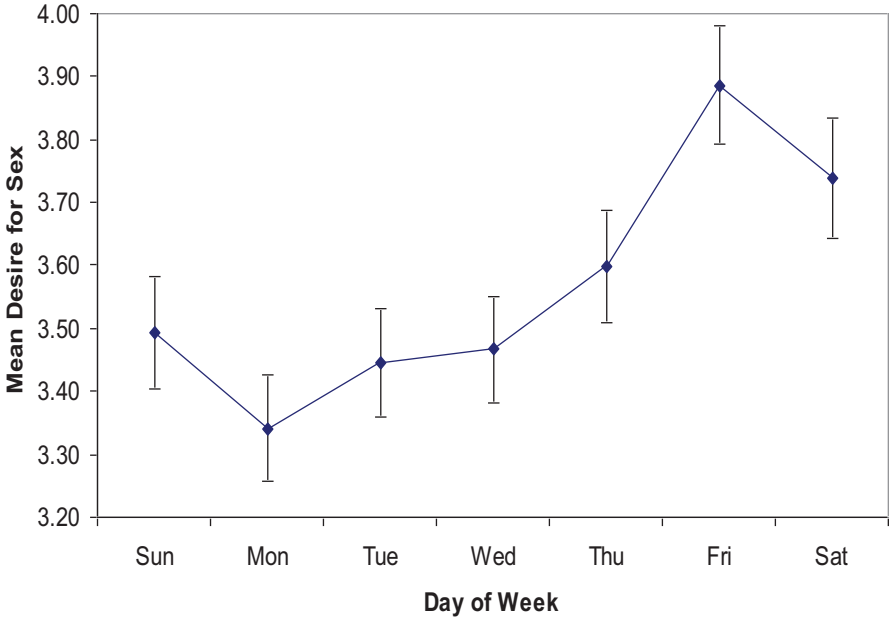

Fig. 6.3 Mean desire for sex aggregated across all women and plotted against day of the week. *Error bars* are SEM

Unlike sexual desire, there was no evidence of a periovulatory peak in sexual behavior. At higher levels, the only significant finding was a negative Level-2 effect of progesterone, meaning that for those women with two cycles of data, sexual frequency tended to be lower in the cycle with higher average progesterone.

Implications of the New Data and Directions for Future Research

The patterns reported in Roney and Simmons (2013) are consistent with those found in females of many nonhuman primates: estradiol was a positive predictor of indices of sexual motivation, whereas progesterone was a negative predictor. This similarity argues for homologous brain mechanisms in the regulation of human and nonhuman sexual motivation, although the extent of modification of those mechanisms for new functions in humans is an open question. At the within-cycle timescale, functions may be similar across species: avoidance of the costs of sexual behavior when conception is absent as a countervailing fitness benefit, as well as relative allocation of attention and motivation to other adaptive problems during non-fecund regions of the cycle. With respect to the latter, for instance, Fessler

(2003) has argued that attention to feeding is downregulated during the follicular phase of ovulatory cycles when mating takes on greater relative importance, but then upregulated in the luteal phase. Trade-offs in the amount of attention and motivation that can be allocated to different tasks may thus help explain the luteal phase decrease in sexual desire, as this region of the cycle may involve an increase in attention to problems unrelated to mating.

One way in which we anticipated modification of regulatory mechanisms in humans was with respect to the role of progesterone. In a nonpregnant state, progesterone is a positive signal of between-cycle fecundity. Because we reasoned that higher sexual motivation may have been functional across days of more fecund cycles in pair-bonding humans, we did not expect progesterone to have the strong inhibitory effects that it is has in most nonhuman mammals. That expectation was not supported, as progesterone was the most consistent negative predictor of desire in our study. Our prediction of a between-cycle positive association between estradiol and sexual motivation was also not supported, as there was no evidence for greater desire or frequency of sexual behavior in the cycle with higher mean estradiol among those women with two cycles of data.

Although we found no evidence for between-cycle effects of hormones, other lines of evidence suggest that they do occur. Dennerstein et al. (2005) found that estradiol was the only endocrine variable to predict longitudinal changes in sexual functioning across the menopausal transition. Likewise, although we found that progesterone was the strongest predictor of sexual desire at the within-cycle timescale, progesterone cannot be the primary regulator of sexual desire or else desire should increase at menopause when progesterone is consistently lower. Instead, the most sensible model appears to be one in which estrogen priming maintains neural networks in a state in which sexual motivation is upregulated, progesterone produces relative declines in such motivation against the background of estrogen priming, and extended estrogen deprivation then produces a general decrease in sexual motivation. Estrogen, then, may have effects at different timescales, with longer-term effects on baseline sexual motivation but also more acute effects associated with rapid increases in estrogen near ovulation. At a between-cycle timescale, sexual motivation may not respond to modest changes in estradiol from cycle to cycle, but likely does respond to more extended periods of estrogen deprivation.

Despite the evidence for within-cycle endocrine predictors of sexual motivation, sexual desire and behavior occurred at all times of the cycle and nonhormonal factors must also be important in explaining variance in libido. Weekend timing—which was uncorrelated with hormone concentrations—was a strong and consistent predictor of both desire and behavior in our study. Given the likely exposure to social stimuli that occurs differentially on weekends in an undergraduate sample, this result suggests that sexual motivation is calibrated simultaneously by exogenous social stimuli and endogenous endocrine signals. The weekend effect was independent of and did not interact with the hormone effects, which suggests that these endogenous and exogenous influences may act separately, at least within the hormonal milieu that characterizes premenopausal women. Retaining the capacity to respond with sexual desire to social stimuli at any point in the cycle (i.e.

independent of hormone concentrations) may be functional given long-term pair-bonds in humans, because desirable long-term partners could be met at any time, and expressions of sexual desire to current partners could have signaling functions that are uncorrelated with current fecundity. Thus, although sex hormones may have main effects in modulating sexual motivation up or down across specific time periods, other variables associated with relationship initiation and maintenance are likely to be important determinants of variance in women's libido.

Calibration of sexual motivation to relationship factors intersects with the broad issue of extended sexuality, and determination of the variables that predict extended sexuality is an important direction for future research on women's sexual motivation. Women's sexual desire tends to decline with increasing relationship length (e.g., Dennerstein et al. 2005; Murray and Milhausen 2012; Pillsworth et al. 2004), which is consistent with the possibility that high sexual motivation has functions related to relationship initiation and pair-bond establishment, since frequent sexual behavior may have been a strong signal of commitment to male partners over most of human history given both the absence of contraception and the large physiological costs associated with human gestation. If true, then high sexual motivation (even on nonfecund days) early in relationships may have functioned as a mate acquisition tactic for women. Once pair-bonds were established and offspring produced, however, attention and motivation may have undergone relative shifts toward more pressing adaptive problems related to parental investment. Even within established reproductive relationships, though, maintenance of some nonreproductive sexual motivation may have functioned to promote continued male investment in the relationship. These speculations regarding the functions and patterns of women's extended sexuality are consistent with available evidence, but more theoretical and empirical work is necessary to understand the mechanisms that regulate nonreproductive sexual motivation.

Conclusion

The mechanisms that regulate sexual motivation should be designed to increase the desire for sex under circumstances in which such desire had higher fitness benefits than costs (including the opportunity costs of alternative behaviors) on average over the course of evolution. In general, the benefit-to-cost ratio of sexual behavior was likely higher on fecund days than on days with little or no conception risk, leading one to expect higher sexual motivation during fecund regions of the cycle. That expectation is borne out across all mammalian species that have been examined. Hormones produced by the ovary can carry information to the brain regarding fecundity, and one can therefore predict based on that information which hormonal signals should promote and inhibit female sexual motivation. Consistent with a fecundity-signaling role, estradiol promotes but progesterone inhibits sexual receptivity and proceptivity in the vast majority of nonhuman mammalian females. Despite this phylogenetic pattern—as well as the physiological homologies between

the reproductive cycles of human and many nonhuman species—it has long been thought that testosterone is the primary regulator of women's libido (for reviews, see Wallen 2001, 2013). As reviewed here, however, both findings regarding the endocrine predictors of changing sexual motivation at menopause (e.g., Dennerstein et al. 2005) and new data on the hormonal correlates of sexual desire in natural cycles (Roney and Simmons 2013) support estradiol as the primary positive regulator of women's sexual motivation. The Roney and Simmons (2013) study likewise identified progesterone as the primary negative predictor of women's desire. It therefore appears that conserved brain mechanisms in women use specific hormonal signals to upregulate sexual motivation during fecund relative to subfecund periods of time.

This chapter has focused on the role of hormonal signals in women's sexual motivation, but there is a need for additional functional analyses of nonhormonal predictors of libido. Theorists have persuasively argued that women's nonreproductive, extended sexuality likely evolved to promote the acquisition of nongenetic, material resources from male partners (e.g., Thornhill and Gangestad 2008). However, the design of the brain mechanisms that govern such sexual behavior—including both the proximate variables that activate increases in sexual motivation as well as the physiological signals that respond to those variables—has not been extensively investigated. Thus, although there is now strong evidence that women have inherited from nonhuman ancestors hormonal mechanisms that calibrate sexual motivation to fluctuations in fecundity, this is only one part of the story, and future research is necessary to systematically test functional hypotheses regarding additional predictors of variance in libido.

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